Tetrahedron: Asymmetry Vol. 3, No. 2, pp. 297-306, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

Enantioselective Synthesis of (1*S*,3*S*,5*R*)-1-Acetoxy-5-benzyloxycyclohexan-3-ol and Its Application to the Synthesis of Compactin Lactone Moiety and Quinic Acid

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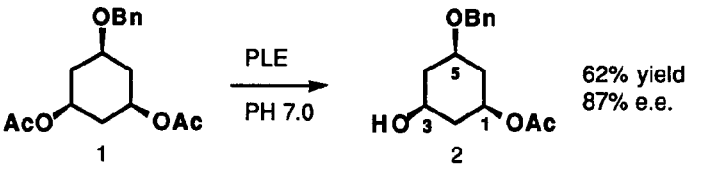
(*Received* 16 *December* 1991)

Abstract: Porcine liver esterase (PLE)-catalyzed asymmetric hydrolysis of *meso*-1,3-*cis*, 3,5-*cis*-1,3-diacetoxy-5-benzyloxycyclohexane **1** afforded (1*S*,3*S*,5*R*)-**2** of 87% e.e. Starting from this compound, compactin lactone moiety **17A** and its C-6 diastereomer **17B** were diastereoselectively synthesized. Furthermore, formal synthesis of quinic acid was also achieved.

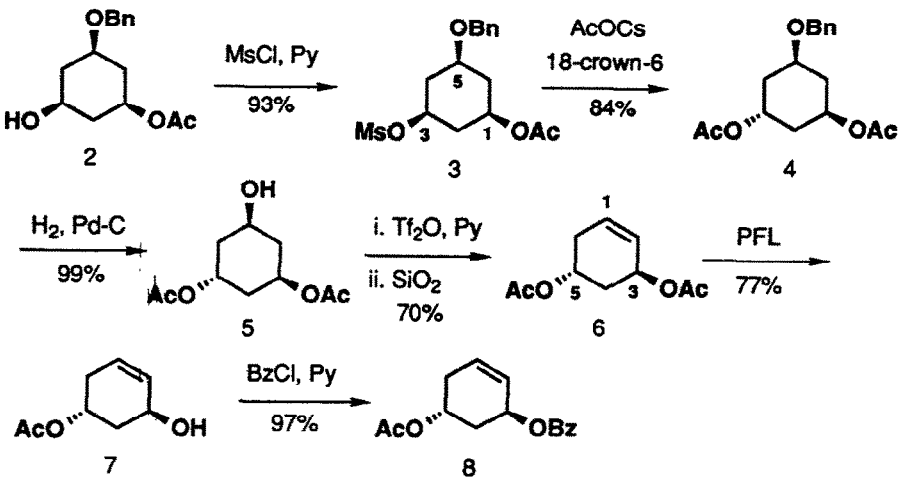
Enantioselective synthesis using an enzymatic procedure has been widely proved to be useful. Especially, asymmetric chiral-induction into *meso*-compounds is one of the most effective methods.[1] In further application of our previous study,[2] we wish to report the enantioselective synthesis of cyclohexanetriol derivatives and its application to the synthesis of compactin lactone moiety and quinic acid.

Porcine liver esterase (PLE)-catalyzed asymmetric hydrolysis of **1** afforded monoacetate **2** (62% isolated yield, 92% conversion yield, 87% e.e.)(Scheme 1). Its enantiomeric excess was estimated by Mosher's method.[3]

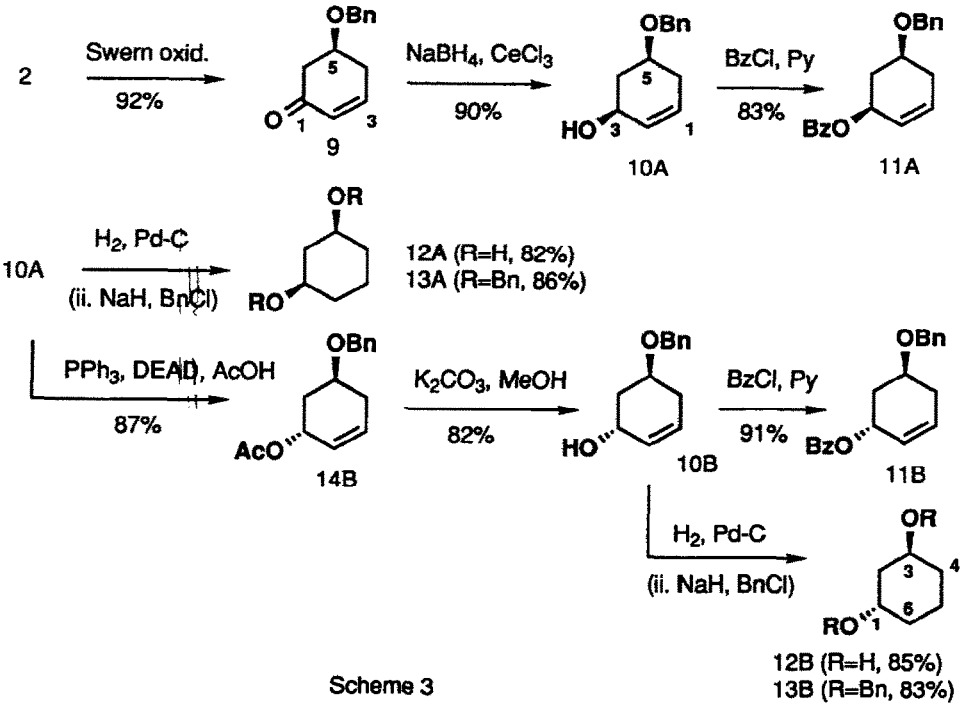


Scheme 1

The absolute configuration of **2**[4] was unambiguously determined by two methods based on CD spectra. One method started from inversion of the 3-hydroxy group in **2** using Ikegami's procedure[5] to afford C_2-symmetric diacetate **4** (78% from **2**) *via* mesylate **3**. After hydrogenolysis of **4** over 10% Pd-C/MeOH into **5** (99%), the dehydrated compound **6** was obtained under mild conditions *via* trifluoromethanesulfonylation and subsequent silica-gel column chromatography.[6] To differentiate the two types of acetates in **6**, *Pseudomonas fluorescens* lipase (PFL)-catalyzed hydrolysis[7] was found to be effective, affording allyl alcohol **7** in 77% yield as a major product with the regioselectivity of 30 : 1. The CD spectrum of the benzoate **8** (97%) derived from **7** showed a negative Cotton effect ($\Delta\varepsilon$=-9.09, 226 nm), which allows us to conclude the absolute configuration of 3-position of **8** to be *S* (Scheme 2).



Scheme 2



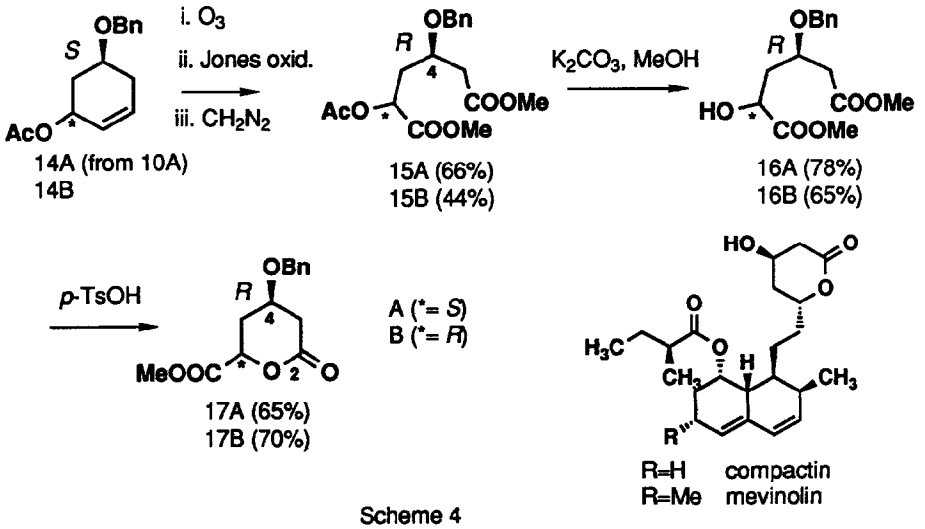
Scheme 3

The other method was undertaken as follows. Compound **2** was converted into enone **9** by Swern oxidation in 92% yield, and subsequent stereoselective reduction by $NaBH_4/CeCl_3$ afforded 3,5-*cis* alcohol **10A**.[8] The relative stereochemistry of **10A** was confirmed by conversion into 1,3-*cis* and *trans*-

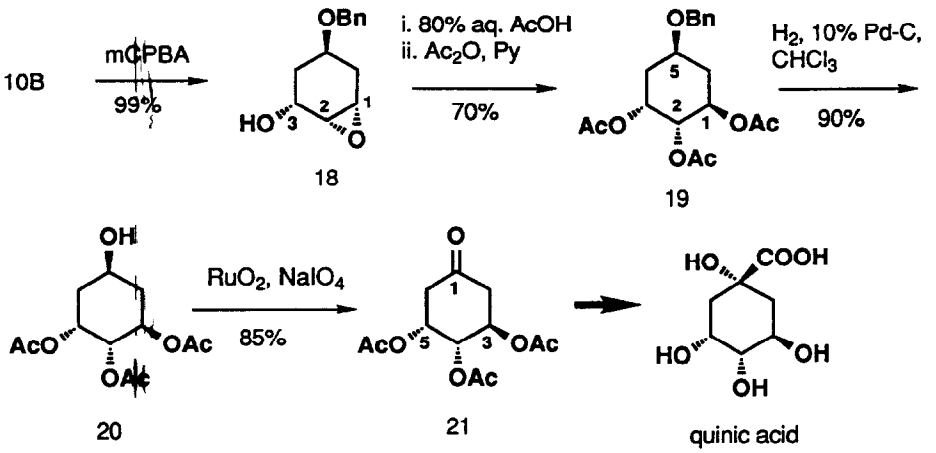
cyclohexanediol derivatives **12,13AB**. Complete hydrogenation of **10A** afforded **12A** (82%), which was converted into **13A** (86%) by usual benzylation. Inversion of the 3-hydroxy group of **10A** by Mitsunobu's method[9] afforded 3,5-*trans*-**14B** (87%). After solvolysis of **14B**, the obtained **10B** was converted into **13B** *via* **12B** in a similar manner to conversion of **10A** into **13A** (Scheme 3). In the ^{1}H and ^{13}C NMR spectra of **13A,B**, it was observed that 1-H was equivalent to 3-H, as were 1-C to 3-C and 4-C to 6-C (**13A**: δ 3.31 (1,3-H), 75.9 (1,3-C), 31.8 (4,6-C); **13B**: δ 3.79 (1,3-H), 74.1 (1,3-C), 30.8 (4,6-C)). The above findings suggest that **13B** takes a twist-boat conformation, and its relative configuration could not be determined from its NMR spectra. On the other hand, specific rotation values of **12A** and **13A** are "zero", and those of **12B** and **13B** are +3.0 and +11.5, respectively. These findings suggest that **12A** and **13A** are achiral (*meso*, 1,3-*cis*), and **12B** and **13B** are chiral (1,3-*trans*).

For determination of the absolute configuration of **10A,B**, these were converted to the corresponding benzoates **11A,B**. The CD spectrum of **11A** showed a negative Cotton effect (Δε=-1.64, 225nm), and that of **11B** showed a positive Cotton effect (Δε=+5.07, 223nm), which suggest the absolute configuration of 3-position in **11A,B** to be *S* and *R*, respectively. From the results of the above two methods, the absolute stereochemistry of **2** was unambiguously concluded to be 1*S*, 3*S*, 5*R*.

Compounds **14A,B** have 1,3-*cis* and/or 1,3-*trans* diol systems and an allylic alcohol system, and are considered to be highly useful chiral syntons for synthetic chemistry. Pursuing the synthetic application of **14A,B**, compactin lactone moiety **17A** and its C-6 epimer **17B** were stereoselectively synthesized. Compactin and mevinolin[10] are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis. The diastereoselective synthesis of their lactone moiety has been easily achieved by using **14A**. By a sequence of two steps of oxidation (ozonolysis and Jones oxid.) and esterification with CH_2N_2, compound **14A** was converted to diester **15A** in 66% yield. Solvolysis of **15A** to **16A** (78%) and subsequent lactonization afforded the target **17A** (65%). By a similar sequence of reactions, **14B** was converted to C-6 epimer **17B** in 20% overall yield (Scheme 4). The structure of each product was confirmed by spectroscopic analyses.



Scheme 4



Scheme 5

As a further synthetic application of **14B**, a formal synthesis of quinic acid was achieved. Quinic acid is of interest in connection with aromatic biosynthesis and has been synthesized by several groups from natural chiral pools such as D-arabinose.[11] Our synthesis started from diastereoselective epoxidation to an allylic alcohol system in **14B** and **10B**. Epoxidation of **14B** with m-chloroperbenzoic acid (mCPBA) afforded diastereomixture of epoxide (α-epoxide : β-epoxide = 3 : 1). On the other hand, reaction of **10B** under the same conditions afforded α-epoxide **18** (99%) in a diastereoselective manner. Stereochemistry of **18** was confirmed by two-dimensional NOESY spectrum of the corresponding acetate (**18-Ac**), in which a cross-peak between 3-H (δ 5.47) and 2-H (δ 3.40) was observed. Ring opening reaction of **18** with aqueous AcOH and following acetylation afforded optically active triacetate **19** (70%), and no *meso*-triacetate was detected. Pd-catalyzed hydrogenolysis of **19** in MeOH afforded a complex mixture, which consisted of partly hydrolyzed products. Reaction in $CHCl_3$ successfully afforded the desired **20** in 90% yield, which could be converted into the corresponding ketone **21** by oxidation with RuO_2 and $NaIO_4$ in 85% yield (Scheme 5). Compound **21** is a synthetic intermediate for quinic acid[11] and shikimic acid.[11b] Spectroscopic data of **21** were identical with those of authentic sample derived from natural quinic acid.[12]

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^1H NMR and ^{13}C NMR spectra were measured by a JEOL JNM-GX 270 spectrometer using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were taken on a JEOL JMD-D-300 spectrometer. Optical rotation was measured on a JASCO DIP-360 polarimeter. CD spectra were measured by a JASCO J-500C spectrometer. For column chromatography, silica gel (Nakarai Tesque, Silica Gel 60, 230-400 mesh) was used. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

(1*S*,3*S*,5*R*)-1-Acetoxy-5-benzyloxy-3-cyclohexanol (2) Porcine liver esterase (Sigma, 1.0 ml) was added to a suspension of **1** (2.0 g) in 0.1M phosphate buffer (pH 7.0, 300 ml) at 30°C. After being stirred for 10 min, the whole was extracted with $CHCl_3$ (50 ml) and AcOEt (50 ml x 2). The combined extracts were washed with brine and dried. The solvent was removed *in vacuo* to afford oily residue, which was purified by silica-gel column chromatography. Substrate **1** (0.64 g, 32%) was recovered from elution of 20% AcOEt-hexane, and **2** (1.07 g, 62%) from elution of 30% AcOEt-hexane as a colorless oil. $[\alpha]_D^{25}$ -5.1 (c=1.85, $CHCl_3$). IR (neat): 3420, 1740, 1610, 1360, 1240, 1060 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.33 (5H, s, Ar-H), 4.74 (1H, tt, *J*=10.7, 4.3 Hz, 1-H), 4.60, 4.51 (1H each, d, *J*=11.7 Hz, CH_2Ph), 3.71 (1H, m, 3-H), 3.49 (1H, tt, *J*=10.4, 4.1 Hz, 5-H), 2.04 (3H, s, OAc). MS *m/z*: 264 (M^+), 221, 186, 145, 91.

(1*R*,3*S*,5*S*)-1-Acetoxy-5-benzyloxy-3-methanesulfonyloxycyclohexane (3) Mesylation of **2** (725 mg) in usual manner (MsCl (1.32 g), pyridine (3 ml), 0°C, 16 h) afforded **3** (876 mg, 93%) as a colorless oil. $[\alpha]_D^{16}$ -0.40 (c=1.58, $CHCl_3$). IR (neat): 1720, 1350, 1220, 1160 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.32 (5H, s, Ar-H), 4.86-4.60 (2H, m, 1,3-H), 4.55 (2H, s, CH_2Ph), 3.46 (1H, m, 5-H), 3.02 (3H, s, OMs), 2.05 (3H, s, OAc). MS *m/z*: 342 (M^+), 186, 91.

(1*R*,3*R*,5*R*)-1,3-Diacetoxy-5-benzyloxycyclohexane (4) A mixed suspension of **3** (875 mg), CsOAc (2.95 g), and 18-crown-6 (798 mg) in benzene (6 ml) was refluxed for 2.5 h. The reaction mixture was diluted with ether (50 ml) and washed with brine, then dried. Purification by silica-gel column chromatography gave **4** (657 mg, 84%) as a colorless oil. $[\alpha]_D^{21}$ -15.0 (c=1.9, $CHCl_3$). IR (neat): 1740, 1610, 1360, 1230, 1035 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.33 (5H, s, Ar-H), 5.30 (1H, tt, *J*=3.5, 3.6 Hz, 3-H), 5.01 (1H, tt, *J*=11.1, 4.3 Hz, 1-H), 4.56, 4.53 (1H each, d, *J*=11.7 Hz, CH_2Ph), 3.75 (1H, tt, *J*=10.6, 4.1 Hz, 5-H), 2.04, 2.03 (3H each, s, OAc x 2). MS *m/z*: 306 (M^+), 263, 246, 200, 91.

(1*R*,3*R*,5*R*)-1,3-Diacetoxy-5-cyclohexanol (5) Hydrogenolysis of **4** (582 mg) in MeOH (5 ml) over 10% Pd-C (1.0 g) afforded **5** (410 mg, 99%) as a colorless oil. $[\alpha]_D^{21}$ -16.7 (c=1.0, $CHCl_3$). IR (neat): 3450, 1740, 1370, 1240, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ:5.29 (1H, m, W_H=8.0 Hz, 3-H), 5.08 (1H, tt, *J*=10.1, 4.3 Hz, 1-H), 4.06 (1H, m, W_H=20 Hz, 5-H), 2.22 (1H, br, OH), 2.06, 2.05 (3H each, s, OAc x 2). MS *m/z*: 216 (M^+), 199, 180, 156, 138.

(3*S*,5*R*)-3,5-Diacetoxy-1-cyclohexene (6) Trifluoromethanesulfonic anhydride (1.61 g) was added to a stirred solution of **5** (410 mg) in pyridine (5 ml) at 0°C. After being stirred for 2 h at 0°C, the reaction mixture was diluted with ether and washed with brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was submitted to silica-gel column chromatography to afford **6** (264 mg, 70%) as a colorless oil. $[\alpha]_D^{21}$ -190 (c=0.5, $CHCl_3$). IR (neat): 1720, 1650, 1360, 1220, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ:5.85 (1H, m, $J_{1,2}$=11.0 Hz, 1-H), 5.79 (1H, m, $J_{1,2}$=11.0 Hz, 2-H) 5.41 (1H, m, 3-H), 5.16 (1H, tt, J=8.4, 4.9 Hz, 5-H), 2.53 (1H, ddd, J=17.8, 4.8, 4.8 Hz, 6-H), 2.31 (1H, m, 6-H), 2.06, 2.05 (3H each, s, OAc x 2). MS *m/z*: 155 (M^+-Ac), 138 (M^+-OAc), 96.

(3*S*,5*R*)-5-Acetoxy-1-cyclohexen-3-ol (7) *Pseudomonas fluorescens* lipase (Amano PS, 200 mg) was added to a suspension of **6** (172 mg) in 0.1M phosphate buffer (pH 7.0, 15 ml) at 30°C. After being stirred for 5.5 h, the whole was extracted with AcOEt. The extract was washed with brine, and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica-gel column chromatography to afford **7** (104 mg, 77%) as a colorless oil. $[\alpha]_D^{14}$ -150 (c=0.7, $CHCl_3$). IR (neat): 3550, 1720, 1650, 1360, 1240, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ:5.84 (1H, m, 2-H), 5.77 (1H, m, 1-H) 5.17 (1H, tt, *J*=7.8, 4.8 Hz, 5-H), 4.38 (1H, m, 3-H), 2.49, 2.08 (1H each, m, 6-H), 2.05 (3H, s, OAc). MS *m/z*: 156 (M^+), 138, 113, 96.

(3*S*,5*R*)-5-Acetoxy-3-benzoyloxy-1-cyclohexene (8) Benzoylation of **7** (33 mg) with benzoyl chloride (59 mg) in pyridine (1 ml) in an usual manner afforded **8** (54 mg, 97%) as a colorless oil. $[\alpha]_D^{14}$ -253 (c=0.5, $CHCl_3$). IR (neat): 1710, 1595, 1360, 1260, 1240 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.13-8.00 (2H, m, Ar-H), 7.66-7.33 (3H, m, Ar-H), 5.94-5.90 (2H, m, 1,2-H), 5.71 (1H, m, 3-H), 5.27 (1H, m, 5-H), 2.62 (1H, m, 6-H), 2.07 (3H, s, OAc). MS *m/z*: 260 (M^+), 226, 200, 138. CD (MeOH): Δε=-9.09 (226 nm, c=7.25 x 10^{-5}).

(*S*)-5-Benzyloxy-2-cyclohexen-1-one (9) Swern oxidation of **2** (818 mg) in usual manner afforded **9** (573 mg, 92%) as a colorless oil. $[\alpha]_D^{23}$ -6.0 (c=2.3, $CHCl_3$). IR (neat): 1720, 1640, 1545, 1430, 1300, 1135 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.32 (5H, m, Ar-H), 6.89 (1H, ddd, *J*=9.0, 4.6, 3.7 Hz, 3-H), 6.07 (1H, dt, *J*=9.0, 1.9 Hz, 2-H), 4.56, 4.58 (1H each, d, *J*=12.2 Hz, $C\underline{H}_2Ph$), 3.91 (1H, m, 5-H). MS *m/z*: 202 (M^+), 158, 108, 91.

(3*S*,5*S*)-5-Benzyloxy-1-cyclohexen-3-ol (10A) $NaBH_4$ (104 mg) was added to a stirred mixture of **9** (470 mg) and $CeCl_3$ (1.15 g) in MeOH (5 ml) at -20°C. The reaction mixture was stirred for 2 h. Usual work-up and subsequent silica-gel column chromatography afforded **10A** (427 mg, 90%) as a colorless oil. $[\alpha]_D^{26}$ -43.0 (c=2.3, $CHCl_3$). IR (neat): 3350, 1640, 1485, 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.32 (5H, m, Ar-H), 5.89 (1H, m, 2-H), 5.71 (1H, m, 1-H), 4.59, 4.53 (1H each, d, *J*=12.0 Hz, $C\underline{H}_2Ph$), 4.13 (1H, m, 3-H), 3.87 (1H, m, 5-H), 2.71 (1H, d, *J*=9.2 Hz, OH). MS *m/z*: 204 (M^+), 186.

(3*S*,5*S*)-3-Benzoyloxy-5-benzyloxy-1-cyclohexene (11A) Benzoylation of **10A** (16 mg) in an usual manner afforded **11A** (20 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ -125 (c=0.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 8.04 (2H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.43 (2H, Ar-H), 7.33 (5H, m, Ar-H), 5.87 (1H, m, 1-H), 5.75 (1H, m, 2-H), 5.66 (1H, m, 3-H), 4.62, 4.60 (1H each, d, *J*=11.9 Hz, $C\underline{H}_2Ph$), 3.78 (1H, m, 5-H). CD (MeOH): Δε=-1.64 (225 nm, c=1.14 x 10^{-4}). HRMS Calcd for $C_{20}H_{20}O_3$ 308.1412; Found 308.1422.

***cis*-Cyclohexane-1,3-diol (12A) and *cis*-1,3-Dibenzyloxycyclohexane (13A)** Compound **10A** (150 mg) was submitted to hydrogenation over 5% Pd-C (200 mg) in MeOH (8 ml) to afford **12A** (70 mg, 82%) as colorless solids. Benzylation of **12A** (27 mg) in usual manner (NaH, $PhCH_2Cl$ in DMSO) gave **13A** (59 mg, 86%) as a colorless oil. **12A**: IR (Nujol): 3350, 1460, 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.80 (2H, m, 1,3-H), 2.43 (2H, brs, OH x 2), 2.17-1.31 (8H, m). MS *m/z*: 116 (M^+). **13A**: IR (neat): 2930, 1500, 1450, 1350 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.33 (10H, m, Ar-H), 4.56 (4H, s, $C\underline{H}_2Ph$ x 2), 3.31 (2H, tt, J=10.6, 4.3Hz, 1,3-H). ^{13}C NMR ($CDCl_3$) δ: 138.9 (4°x2), 128.3 (3°x4), 127.5 (3°x4), 127.4 (3°x2), 75.9 (3°x2), 70.0 (2°x2), 38.9 (2°), 31.8 (2°x2), 20.8 (2°). MS *m/z*: 296 (M^+), 270, 188, 91.

(3*S*,5*S*)-3-Acetoxy-5-benzyloxy-1-cyclohexene (14A) Acetylation of **10A** (176 mg) in usual manner (Ac_2O (0.28 ml), 4-dimethylaminopyridine (10 mg) in pyridine (1.5 ml) at room temperature for 6 h) afforded **14A** (190 mg, 90%) as a colorless oil. $[\alpha]_D^{22}$ -50.0 (c=1.5, $CHCl_3$). IR (neat): 1730, 1360, 1240, 1100, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.33 (5H, m, Ar-H), 5.81 (1H, dddd, *J*=9.9, 4.6, 1.7, 1.7 Hz, 1-H), 5.61 (1H, m, $J_{1,2}$=9.9 Hz, 2-H), 5.41 (1H, m, 3-H), 4.60, 4.55 (1H each, d, *J*=10.9 Hz, $C\underline{H}_2Ph$), 3.70 (1H, m, 5-H), 2.07 (3H, s, OAc), 1.70 (1H, ddd, *J*=11.2, 9.2, 9.2 Hz, 4-H). MS *m/z*: 246 (M^+), 203, 186.

(3*R*,5*S*)-3-Acetoxy-5-benzyloxy-1-cyclohexene (14B) Diethyl azodicarboxylate (1 ml) was added to a stirred solution of **10A** (150 mg), AcOH (220 mg) and PPh_3 (960 mg) in THF (7 ml) at 0°C. After being stirred for 8 h at room temperature, usual work-up and purification with silica-gel column chromatography afforded **14B** (157 mg, 87%) as a colorless oil. $[\alpha]_D^{22}$ +67.0 (c=1.0, $CHCl_3$). IR (neat): 1730, 1370, 1240,

1100, 1050 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.35-7.26 (5H, m, Ar-H), 5.88 (1H, dddd, *J*=9.9, 5.0, 2.6, 0.7 Hz, 1-H), 5.76 (1H, m, $J_{1,2}$=9.9Hz, 2-H), 5.42 (1H, m, 3-H), 4.60, 4.58 (1H each, d, *J*=11.9 Hz, $C\underline{H}_2Ph$), 3.84 (1H, m, 5-H), 2.04 (3H, s, OAc),1.90 (1H, ddd, *J*=13.5, 10.2, 5.0 Hz). MS *m/z* 246 (M^+), 186, 155, 113.

(3*R*,5*S*)-5-Benzyloxy-1-cyclohexen-3-ol (10B) and **(3*R*,5*S*)-3-Benzoyloxy-5-benzyloxy-1-cyclohexene (11B)** Solvolysis of **14B** (40 mg) with K_2CO_3 (7 mg) in MeOH (1.5 ml) gave **10B** (27 mg, 82%) as a colorless oil. $[\alpha]_D^{24}$ +40.2 (c=1.0, $CHCl_3$). IR (neat): 3375, 1650, 1500, 1360, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.37-7.24 (5H, m, Ar-H), 5.84-5.73 (2H, m, 1,2-H), 4.60, 4.59 (1H each, d, *J*=11.9 Hz, $C\underline{H}_2Ph$), 4.42 (1H, br s, 3-H), 3.85 (1H, m, 5-H), 1.89 (1H, ddd, *J*=13.2, 9.9, 4.6 Hz). MS *m/z* 204 (M^+), 186, 142, 113, 91. Benzoylation of **10B** (17 mg) in usual manner afforded **11B** (24 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ +100 (c=0.8, $CHCl_3$). IR (neat): 1715, 1600, 1500, 1450, 1270, 1200 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.00 (2H, m), 7.56 (1H, m), 7.46-7.27 (7H, m), 5.97-5.85 (2H, m, 1,2-H), 5.67 (1H, m, 3-H), 4.64, 4.60 (1H each, d, *J*=11.9 Hz, $C\underline{H}_2Ph$), 3.95 (1H, m, 5-H), 2.55 (1H, m, *J*gem=18.1 Hz), 2.25 (1H, m, *J*gem=13.8 Hz), 2.16 (1H, m, *J*gem=18.1 Hz), 2.00 (1H, m, *J*gem=13.8 Hz). MS *m/z* 308 (M^+), 241, 217, 202, 186. CD (MeOH): Δε=+5.07 (223 nm, c=5.24x10^{-5}). HRMS Calcd for $C_{20}H_{20}O_3$ 308.1412; Found 308.1405.

(*S*,*S*)-Cyclohexane-1,3-diol (12B) and **(*S*,*S*)-1,3-Dibenzyloxycyclohexane (13B)** Compounds **12B** and **13B** were obtained from **10B** in a similar manner to conversion of **10A** into **12A** and **13A**. **12B**: 85% yield; A colorless oil. $[\alpha]_D^{25}$ +3.0 (c=1.0, $CHCl_3$). IR (neat): 3350, 1440, 1360, 1090 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.12 (2H, m, 1,3-H), 1.80-1.25 (10H,m). MS *m/z* 116 (M^+), 98, 80. **13B**: 83% yield; $[\alpha]_D^{22}$ +11.5 (c=1.0, $CHCl_3$). IR (neat): 2925, 1500, 1450, 1360 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.34-7.24 (10H, m, Ar-H), 4.52, 4.48 (2H each, d, *J*=11.8 Hz, 3.79 (2H, m, 1,3-H), 1.86 (2H, t, *J*=5.3 Hz, 2-H). ^{13}C NMR ($CDCl_3$) δ: 139.2 (4°x2), 128.3 (3°x4), 127.5 (3°x4), 127.3 (3°x2), 74.1 (3°x2), 70.0 (2°x2), 36.5 (2°), 30.8 (2°x2), 19.3 (2°). MS *m/z*: 296 (M^+), 188, 91.

Synthesis of compactin lactone moiety (17A) and its diastereomer (17B):

(2*S*,4*R*)-Dimethyl 2-Acetoxy-4-benzyloxyhexanedioate (15A) and **(2*R*,4*R*)-isomer (15B)** Ozonolysis of **14A** (376 mg) and reductive work-up with zinc powder afforded crude dialdehyde, which was converted to dicarboxylic acid by Jones oxidation. Esterification with CH_2N_2 gave **15A** (344 mg, 66% from **14A**) as a colorless oil. $[\alpha]_D^{26}$ -1.0 (c=5.0, $CHCl_3$). IR (neat): 1740, 1440, 1375, 1220, 1170, 1090 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.32-7.28 (5H, m, Ar-H), 5.17 (1H, t, *J*=5.8 Hz, 2-H), 4.53, 4.48 (1H each, d, *J*=10.9 Hz, $C\underline{H}_2Ph$), 4.10 (1H, m, 4-H), 3.68, 3.59 (3H each, s, COOMe x 2), 2.68, 2.54 (1H each, *J*=15.6, 6.3 Hz, 5-H), 2.29-2.04 (2H, m, 3-H), 2.14 (3H, s, OAc). MS *m/z*: 338 (M^+), 307, 265, 132. Compound **15B** was obtained from **14B** in a similar manner as a colorless oil in 44% yield. $[\alpha]_D^{20}$ +21.0 (c=4.3, $CHCl_3$). IR (neat): 1740, 1435, 1370, 1220, 1090 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.35-7.27 (5H, m, Ar-H), 5.19 (1H, dd, *J*=10.4, 3.1 Hz, 2-H), 4.61, 4.41 (1H each, d, *J*=11.2 Hz, $C\underline{H}_2Ph$), 4.00 (1H, m, 4-H), 3.71, 3.70 (3H each, s, COOMe x 2), 2.72 (1H, dd, *J*=15.2, 5.6 Hz, 5-H), 2.54 (1H, dd, *J*=15.2, 6.3 Hz, 5-H), 2.19-1.98 (2H, m, 3-H), 2.13 (3H, s, OAc). MS *m/z*: 338 (M^+), 307, 265, 232, 132.

(2*S*,4*R*)-Dimethyl 4-Benzyloxy-2-hydroxyhexanedioate (16A) and **(2*R*,4*R*)-isomer (16B)** K_2CO_3 (34 mg) was added to a stirred solution of **15A** (166 mg) in MeOH (2.5 ml) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with ether and washed with brine, then dried. Purification

by silica-gel column chromatography afforded **16A** (113 mg, 78%) as a colorless oil. $[\alpha]_D^{26}$ +8.1 (c=1.0, $CHCl_3$). IR (neat): 3470, 1735, 1435, 1220, 1165, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.34-7.27 (5H, m, Ar-H), 4.53, 4.42 (1H each, d, *J*=10.9 Hz, C<u>H</u>$_2$Ph), 4.31 (1H, dd, *J*=9.2, 4.9 Hz, 2-H), 4.16 (1H, m, 4-H), 3.68, 3.58 (3H each, s, COOMe x 2), 2.71 (1H, dd, *J*=15.2, 5.9 Hz, 5-H), 2.58 (1H, dd, *J*=15.2, 6.6 Hz, 5-H), 2.12-2.07 (2H, m, 3-H). MS *m/z*: 296 (M^+), 264, 219, 205. Compound **16B** was obtained from **15B** in a similar manner as a colorless oil in 65% yield. $[\alpha]_D^{20}$ +4.6 (c=4.3, $CHCl_3$). IR (neat): 3480, 1735, 1435, 1365, 1210, 1165, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.33-7.27 (5H, m, Ar-H), 4.64, 4.56 (1H each, d, *J*=11.0 Hz, C<u>H</u>$_2$Ph), 4.41 (1H, m, 2-H), 4.18 (1H, m, 4-H), 3.76, 3.68 (3H each, s, COOMe x 2), 3.02 (1H, d, *J*=6.0 Hz, OH), 2.71 (1H, dd, *J*=15.2, 5.9 Hz, 5-H), 2.57 (1H, dd, *J*=15.2, 6.3 Hz, 5-H), 2.11 (1H, ddd, *J*=14.4, 9.4, 2.8 Hz, 3-H), 1.83 (1H, ddd, *J*=14.4, 9.6, 3.3 Hz, 3-H). MS *m/z*: 296 (M^+), 264, 190, 158.

(4*R*,6*S*)-4-Benzyloxy-6-methoxycarbonyltetrahydro-2-pyranone (17A) and **(4*R*,6*R*)-isomer (17B)** A mixed solution of **16A** (40 mg) and *p*-TsOH (5 mg) in benzene (5 ml) was stirred at 50°C for 20 h. Usual work-up and purification by preparative TLC afforded **17A** (23 mg, 65%) as a colorless oil. $[\alpha]_D^{24}$ +12.8 (c=0.6, $CHCl_3$). IR (neat): 1760, 1440, 1365, 1240, 1180, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.39-7.30 (5H, m, Ar-H), 5.15 (1H, dd, *J*=8.9, 4.6 Hz, 6-H), 4.56 (2H, s, C<u>H</u>$_2$Ph), 3.99 (1H, m, 4-H), 3.80 (3H, s, COOMe), 2.77 (2H, d, *J*=4.9 Hz, 3-H), 2.32 (1H, ddd, *J*=14.2, 4.9, 4.9 Hz, 5-H), 2.15 (1H, ddd, *J*=14.2, 8.6, 3.5 Hz, 5-H). MS *m/z*: 264 (M^+), 178, 108, 97. HRMS Calcd for $C_{14}H_{16}O_5$ 264.0997; Found 264.0991. Compound **17B** was obtained from **16B** in a similar manner as a colorless oil in 70% yield. $[\alpha]_D^{20}$ -11.5 (c=0.5, $CHCl_3$). IR (neat): 1750, 1435, 1370, 1345, 1205, 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.38-7.27 (5H, m, Ar-H), 4.93 (1H, dd, *J*=5.6, 4.9 Hz, 6-H), 4.52, 4.45 (1H each, d, *J*=11.7 Hz, C<u>H</u>$_2$Ph), 4.00 (1H, m, 4-H), 3.62 (3H, s, COOMe), 2.81 (1H, d, *J*=5.3 Hz, 3-H), 2.80 (1H, d, *J*=3.6 Hz, 3-H), 2.52 (1H, ddd, *J*=14.4, 4.9, 4.9 Hz, 5-H), 2.31 (1H, ddd, *J*=14.4, 5.6, 3.5 Hz, 5-H). MS *m/z*: 264 (M^+), 205, 158. HRMS Calcd for $C_{14}H_{16}O_5$ 264.0997; Found 264.1001.

Formal Synthesis of Quinic Acid:

(1*S*,2*R*,3*R*,5*R*)-5-Benzyloxy-1,2-epoxycyclohexan-3-ol (18) and **Its Acetate (18-Ac)** m-Chloroperbenzoic acid (256 mg) was added to a stirred solution of **10B** (220 mg) in CH_2Cl_2 (4 ml) at 0°C. After being stirred for 20 h at room temperature, the reaction mixture was worked up in an usual manner. Purification of the crude product by silica-gel column chromatography afforded **18** (261 mg, 99%) as a colorless oil. $[\alpha]_D^{25}$ +18.6 (c=4.4, $CHCl_3$). IR (neat): 3400, 1410, 1340, 1250, 1050 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.37-7.23 (5H, m, Ar-H), 4.50, 4.44 (1H each, d, *J*=11.9 Hz, C<u>H</u>$_2$Ph), 4.32 (1H, br s, 3-H), 3.67 (1H, m, 5-H), 3.37 (2H, m, 1,2-H), 2.26 (1H, br, OH), 2.10-1.95 (3H, m), 1.55 (1H, ddd, *J*=13.5, 9.2, 2.0 Hz, 4-H). MS *m/z*: 220 (M^+), 184, 158, 108. Usual acetylation of **18** afforded the corresponding acetate (**18-Ac**) in 90% yield as a colorless oil. $[\alpha]_D^{25}$ +19.5 (c=3.4, $CHCl_3$). IR (neat): 1725, 1365, 1235, 1065, 1035 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.35-7.27 (5H, m, Ar-H), 5.47 (1H, ddd, *J*=10.2, 5.6, 2.0 Hz, 3-H), 4.55, 4.44 (1H each, d, *J*=11.9 Hz, C<u>H</u>$_2$Ph), 3.70 (1H, m, 5-H), 3.40 (1H, m, 2-H), 3.30 (1H, m, 1-H), 2.11 (3H, s, OAc), 2.08-2.04 (3H, m), 1.63 (1H, m, 4-H). FDMS *m/z*: 262 (M^+), 232, 213.

(1*R*,2*S*,3*R*,5*R*)-1,2,3-Triacetoxy-5-benzyloxycyclohexane (19) A solution of **18** (210 mg) in 80% aqueous AcOH (2.5 ml) was stirred for 22 h at room temperature. After removal of the solvent *in vacuo*, reagents for acetylation (pyridine (2 ml), Ac_2O (2 ml) and 4-dimethylaminopyridine (30 mg)) was added at 0°C. The whole was stirred for 22 h at room temperature. Usual work-up and purification afforded **19** (241 mg,

70%) as a colorless oil. $[\alpha]_D^{25}$ -16.7 (c=3.1, $CHCl_3$). IR (neat): 1730, 1365, 1220, 1045 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.37-7.27 (5H, m, Ar-H), 5.47 (1H, dt, *J*=2.9, 3.3 Hz, 3-H*eq*), 5.14 (1H, ddd, *J*=10.9, 9.9, 4.9 Hz, 1-H*ax*), 4.93 (1H, dd, *J*=9.9, 3.3 Hz, 2-H*ax*), 4.53, 4.51 (1H each, d, *J*=11.5 Hz, $C\underline{H}_2Ph$), 3.82 (1H, tt, *J*=10.9, 4.3 Hz, 5-H*ax*), 2.53 (1H, m, 6-H*eq*), 2.25 (1H, m, 4-H*eq*), 2.06, 2.03, 2.00 (3H each, s, OAc x 3), 1.68 (1H, ddd, *J*=13.5, 10.9, 3.3 Hz, 4-H*ax*), 1.54 (1H, dt, *J*=11.2, 10.9 Hz, 6-H*ax*). FDMS *m/z*: 364 (M^+), 305, 183, 91. HRMS Calcd for $C_{19}H_{24}O_7$ 364.1522; Found 364.1515.

(1*R*,2*S*,3*R*,5*R*)-1,2,3-Triacetoxycyclohexan-5-ol (20) Hydrogenolysis of **19** (172 mg) over 10% Pd-C (202 mg) in $CHCl_3$ (30 ml) afforded **20** (117 mg, 90%) as a colorless oil. $[\alpha]_D^{27}$ -18.2 (c=1.8, $CHCl_3$). IR ($CHCl_3$): 3300, 1735, 1365, 1220, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.46 (1H, ddd, *J*=3.3, 2.9, 2.7 Hz, 3-H*eq*), 5.17 (1H, ddd, *J*=10.9, 9.9, 4.6 Hz, 1-H*ax*), 4.93 (1H, dd, *J*=9.9, 3.3 Hz, 2-H*ax*), 4.13 (1H, tt, *J*=10.6, 4.0 Hz, 5-H*ax*), 2.41 (1H, m, 6-H*eq*), 2.17 (1H, m, 4-H*eq*), 2.09, 2.05, 2.01 (3H each, s, OAc x 3), 1.88 (1H, br s, OH), 1.66 (1H, ddd, *J*=13.9, 10.6, 2.7 Hz, 4-H*ax*), 1.53 (1H, ddd, *J*=12.2, 10.9, 10.6 Hz, 6-H*ax*). FDMS *m/z*: 275 (M^++1), 257, 215.

(3*R*,5*R*)-3,4,5-Triacetoxycyclohexanone (21) An 0.28 M aqueous solution of $NaIO_4$ (1.7 ml) was added to a mixed suspension of **20** (99 mg) and RuO_2 (50 mg) in CCl_4 (2 ml) at room temperature. After being vigorously stirred for 2 h, the above $NaIO_4$ solution (1 ml) was added, and the whole was stirred for another 2 h. The reaction was quenched with isopropanol (0.5 ml). The whole was filtered, and washed with ether (10 ml). The combined filtrates were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded crude solids which were recrystalized from ether at -50°C to afford **21** (82 mg, 85%) as colorless solids. $[\alpha]_D^{19}$ -68.0 (c=1.8, benzene), (authentic sample of **21** derived from natural quinic acid: $[\alpha]_D^{17}$ -72.0 (c=1.5, benzene)).[12] mp 76-77°C. ^1H NMR (C_6D_6) δ: 5.56 (1H, m, 5-H*eq*), 5.36 (1H, ddd, *J*=10.9, 9.9, 5.7 Hz, 3-H*ax*), 5.05 (1H, dd, *J*=9.9, 3.3 Hz, 4-H*ax*), 2.60 (1H, ddd, *J*=15.2, 4.6, 1.7 Hz), 2.40-2.08 (3H, m), 1.75, 1.65, 1.63 (3H each, s, OAc x 3).

References and Notes

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